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Some Metal(II) Chelates of 4-(*m*-Aminophenyl)-2-formylpyridine Thiosemicarbazone: their Preparation, Characterization and Antitumour Activity

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Abstract

Complexes of Co(II), Ni(II), Cu(II), Zn(II) and Pt(II) with 4-(*m*-aminophenyl)-2-formylpyridine thiosemicarbazone (4-*m*-NH_2ph-2-pytsc-H) were isolated and characterized by elemental analysis, conductance measurements, magnetic susceptibilities (from room temperature to liquid N_2 temperature), diffuse reflectance and infrared studies. On the basis of these studies a distorted trigonal-bipyramidal structure for [M(4-*m*-NH_2ph-2-pytsc-H)Cl_2] (M = Co(II), Ni(II) or Cu(II)), [Zn(4-*m*-NH_2ph-2-pytsc-H)$(OAc)_2$] and a square-planar structure for [Pt(4-*m*-NH_2ph-2-pytsc)Cl] are suggested. All these metal(II) chelates were screened for their antitumour activity in the P388 lymphocytic leukaemia test system in mice, and were found to possess no significant activity at the dosages employed.

Introduction

Considerable attention has focused upon the antitumour activity of a variety of metal complexes and complexing agents [1–3]. Although the activity of platinum complexes is well documented [4], a number of complexes of essential metals, particularly first-row transition metals, also possess some degree of cytotoxic activity [5]. Following a series of reports [6] on α(N)-heterocyclic carboxaldehyde thiosemicarbazones and their metal complexes, investigations to discover more potent antitumour metal chelates were initiated [7]. In this paper we report the isolation, characterization and antitumour activity of some metal(II) chelates of 4-(*m*-aminophenyl)-2-formylpyridine thiosemicarbazone.

Experimental

4-(*m*-Aminophenyl)-2-formylpyridine thiosemicarbazone was obtained as a gift from the National Cancer Institute and has been previously characterized [8]. Potassium tetrachloroplatinate(II) (Aldrich Chemical Co.) was used as such. Other metal(II) salts and solvents were reagent grade chemicals.

Synthesis

All the metal(II) chelates were isolated by the following general method. A suspension of 4-(*m*-aminophenyl)-2-formylpyridine thiosemicarbazone (0.271 g, 1 mmol) in methanol (20 ml) was added to the solution of metal(II) salt (1 mmol) in the minimum amount of methanol or an aqueous solution of K_2PtCl_4 (0.415 g, 1 mmol) and the mixture was stirred at room temperature for about 30 min. The thiosemicarbazone gradually dissolved and the crystalline solid of the complexes separated from the solution. The solid was filtered, washed with methanol or water (in case of Pt(II) only) and diethylether and dried over P_2O_5 under vacuum. Yield 75–85%.

Elemental analysis for carbon, hydrogen and nitrogen were performed by the Microanalytical Laboratory of C.D.R.I., Lucknow, India. The analytical data are given in Table I.

Physical Measurements

Physical measurements were carried out as described previously [7].

Results and Discussion

The infrared spectrum of 4-(*m*-aminophenyl)-2-formylpyridine thiosemicarbazone (4-*m*-NH_2ph-2-pytsc-H) exhibits ν(NH) absorption bands at 3380s and 3210s cm^{-1} but no ν(SH) at *ca.* 2570 cm^{-1} is observed. Thus, in the solid state, 4-*m*-NH_2ph-2-pytsc-H exists in the thione form (**I**). However, in solution the compound probably exists in equilibrium with the tautomeric forms (**Ia**). Tautomer

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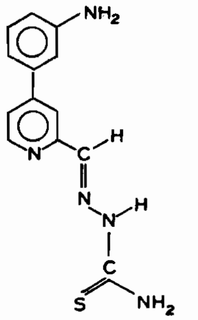
TABLE I. Analytical and Magnetic Data of Metal(II) Complexes of 4-*m*-Aminophenyl-2-formylpyridine Thiosemicarbazone.

Compound	Colour	Found			Calculated			μ_{eff} μ_β at RT	θ, K
		C%	H%	N%	C%	H%	N%		
1 $[Co(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc\text{-}H)Cl_2]$	Brown	38.94	3.24	17.50	38.90	3.24	17.45	4.43	−4
2 $[Ni(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc\text{-}II)Cl_2]$	Greenish yellow	38.90	3.26	17.45	38.93	3.24	17.46	3.25	−3
3 $[Cu(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc\text{-}H)Cl_2]$	Green	38.40	3.21	17.28	38.46	3.20	17.26	1.84	−4
4 $[Zn(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc\text{-}H)(OAc)_2]$	Yellow	48.32	4.50	16.60	48.29	4.49	16.57	Diamagnetic	
5 $[Pt(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc)Cl]$	Dark red	31.12	2.42	13.99	31.16	2.39	13.98	Diamagnetic	

(**Ia**) by the loss of a thiol proton may act as single charged tridentate ligand, coordinating through the mercapto sulphur, the central nitrogen and the pyridine nitrogen atoms. When the suspension of the free ligand 4-*m*-NH_2ph-2-pytsc-H is stirred with methanolic or aqueous solution of metal(II) salt, it yields the coloured crystalline complexes of the formula $[M(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc\text{-}H)Cl_2]$ (M = Co(II), Ni(II) or Cu(II)), $[Zn(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc\text{-}H)(OAc)_2]$ and $[Pt(4\text{-}m\text{-}NH_2ph\text{-}2\text{-}pytsc)Cl]$. These metal(II) complexes are quite stable at room temperature and do not show any decomposition after a long period of standing. All the complexes are insoluble in water, and partially soluble in a large number of solvents of low coordinating ability such as CCl_4, CS_2, C_6H_6, $C_6H_5NO_2$, $CHCl_3$, tetrahydrofuran, diethylether and acetonitrile. The complexes are soluble in a number of solvents of moderate-to-good coordinating ability, such as dimethylformamide, dimethylsulphoxide, methanol, ethanol and pyridine. The molar conductance of the complexes in methanol at *ca.* 10^{-3} M lie in the 10.0–13.60 ohm^{-1} cm^2 mol^{-1} range, indicating their non-electrolytic behaviour in solution [9]. Although the complexes do not possess sharp melting points, they decompose above 200 °C.



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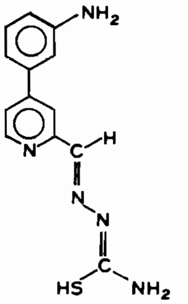
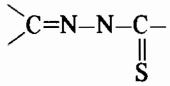


Ia

The assignments of some of the infrared spectral bands of free 4-*m*-NH_2ph-2-pytsc-H and its metal(II) chelates are reported in Table II. In the NH stretching region, the high frequency component ν_{as}(NH) remains practically unchanged on coordination, relative to that of the free ligand, while the low frequency component is shifted to high frequency by about 60 cm^{-1}. This suggests that there is no direct bond formation between the nitrogen atom of the amino group and the metal(II) ion, as partly confirmed by the high frequency shift of the scissors deformation of the NH_2 group ($\Delta\delta(NH_2) \simeq 20$ cm^{-1}) and of the antisymmetric and symmetric stretches ν_{as}(CN) and ν_s(CN) of the $-\mathrm{N}-\underset{\underset{\mathrm{S}}{\|}}{\mathrm{C}}-\mathrm{N}-$ group ($\Delta\nu_{as}(CN) \simeq 40$ cm^{-1}, $\Delta\nu_s(CN) \simeq 25$ cm^{-1}). The coordination of the azomethine nitrogen to the metal(II) ion is indicated by the shifting of the band chiefly assigned [10] to the N–N stretch. The spectra of the metal(II) chelates show a low-frequency shift of ν(N–N) from 1060 cm^{-1} for

TABLE II. Selected Infrared Vibrations of 4-*m*-Aminophenyl-2-Formylpyridine Thiosemicarbazone and Metal(II) Complexes (cm^{-1}).

4-*m*-NH_2ph-2-pytsc-H	Co	Ni	Cu	Zn	Pt	Assignment
3380s	3380s	3375s	3380s	3380s	3370s	ν_{as}(NH)
3210s	3265s	3270s	3260s	3270s	3265s	ν_s(NH)
1620s	1638s	1640s	1635s	1640s	1640s	δ(NH)
1540m	1575m	1580m	1575m	1580s	1580s	ν(C=N)
1498	1480s	1475s	1480s	1478s	1480s	ν(CN) + δ(NH)
1460sb	1465s	1460sb	1460s	1465w	1470m	Band III ring
1300m	1330mb	1340mb	1335s	1350m	1320mb	ν(CS) + ν(CN) + δ(NH_2)
1060s	1050s	1045s	1045s	1040s	1045s	ν(N–N)
828s	788s	785s	785s	795s	726s	ν(CS)

ligand to approximately 1040 cm^{-1} in the spectra of metal(II) complexes. On the other hand, the ν(C=N) frequency, 1540 cm^{-1} in the spectrum of the ligand, is shifted to higher frequency by about 40 cm^{-1}. These changes in the frequencies of the  $>C{=}N{-}N{-}\underset{\underset{\displaystyle S}{\|}}{C}{-}$ group are typical of the coordination of a ligand to a metal through the azomethine nitrogen atom.

In most thiosemicarbazone complexes, the second donor is the sulphur atom [11]. If coordination occurs through the thioamide sulphur atom, the ν(CS) will shift to lower frequency and the coupled δ(NH) and ν(CN) should shift in opposite directions. Consequently the amide ν(CN) + δ(NH) may exhibit a decrease, due to drainage of the electrons from the nitrogen atom. An inspection of the infrared spectral data (Table II) shows that the bonding of 4-*m*-NH$_2$-ph-2-pytsc-H indeed occurs through the thioamide sulphur atom. On coordination, ν(CS) is shifted by approximately 100 cm^{-1} to lower frequency in the Pt(II) complex and approximately 40 cm^{-1} in the Co(II), Ni(II), Cu(II) and Zn(II) complexes. This situation is most probably consistent with different geometries of these complexes (*vide infra*). The coordination of pyridine nitrogen atom to the metal(II) ion is indicated by the shifting and splitting of the ring vibrations as is usually observed in other metal(II) pyridine complexes [12].

In the far-infrared spectral region the Co(II), Ni(II), Cu(II) and Zn(II) complexes exhibit bands at *ca.* 290s and 260s cm^{-1} which are assigned [13, 14] to ν(M–S) and ν(M–N) stretching vibrations, respectively. In the Pt(II) complex the ν(M–S) and ν(M–N) vibrations are observed at 280s and 265s cm^{-1}, respectively [11]. In all these complexes the ν(M–N) pyridine [15] appeared at *ca.* 230s cm^{-1} and ν(M–Cl) [M = Co(II), Ni(II) or Cu(II)] at 246s cm^{-1} [13, 14, 16]. Although these assignments are tentative because of the possibility of accidental co-incidences and intensity variations, the position of the bands is consistent with five-(Co(II), Ni(II), Cu(II) or Zn(II)) and four-(Pt(II)) coordinate geometries [13–16]. The appearance of ν_{as}(COO) and ν_s(COO) vibrations at 1560sb and 1420vs cm^{-1}, respectively, suggests the monodentate coordination of acetato groups in the Zn(II) complex [17].

The magnetic susceptibilities of Co(II), Ni(II) and Cu(II) complexes were measured as a function of temperature from room temperature down to liquid N$_2$ temperature. The μ_{eff} values at room temperature with Weiss constant, θ, are reported in Table I. The Zn(II) and Pt(II) complexes are diamagnetic. The μ_{eff} values of Co(II) and Ni(II) complexes are in the range expected for five-coordinate complexes [14, 18, 19]. The μ_{eff} values of the Cu(II) complex are very close to spin-only for one unpaired electron and are in the range normally observed for copper(II) complexes having an orbitally non-degenerate ground state [20]. In fact, no significant conclusion can be drawn from the magnetic data regarding the stereochemistry of [Cu(4-*m*-NH$_2$ph-2-pytsc-H)Cl$_2$] complex, since there is little difference in magnitude between magnetic moments of various configurations in copper(II) complexes [20].

The UV spectrum of free ligand 4-*m*-NH$_2$ph-2-pytsc-H shows sharp bands at 27 027, 28 010, 30 765, 32 756, 35 715 and 40 000 cm^{-1}, which are assigned to $\pi \rightarrow \pi^*$ transitions. The position of the bands suggests the anti (E)-form (**I**) of the free ligand in the solid state [21]. The UV spectra of all metal(II) complexes exhibit the bands of varying intensity almost at the same positions as in the anti-form of the ligand, suggesting that the ligand has anti (E)-configuration in the solid state in all the metal(II) complexes.

The diffuse reflectance spectrum of the Co(II) complex in the visible region (Fig. 1(a)) is very similar to the spectra of [Co(Me$_6$tren)X]X [Me$_6$-tren = tris(2-dimethylaminoethyl)amine] which are five-coordinate and which have C_{3v} symmetry [22, 23]. Thus the spectral bands observed at 4490, 4825, 5810, 12 690, 17 240 and 19 230 cm^{-1} in [Co(4-*m*-NH$_2$ph-2-pytsc-H)Cl$_2$] are assigned to $^4A_2 \rightarrow {}^4A_1(F)$, $^4A_2 \rightarrow {}^4A_2(F)$, $^4A_2 \rightarrow {}^4E(F)$, $^4A_2 \rightarrow {}^4E$, $^4A_2 \rightarrow {}^4A_2(P)$ and $^4A_2 \rightarrow {}^4E(P)$ transitions, respectively [24].

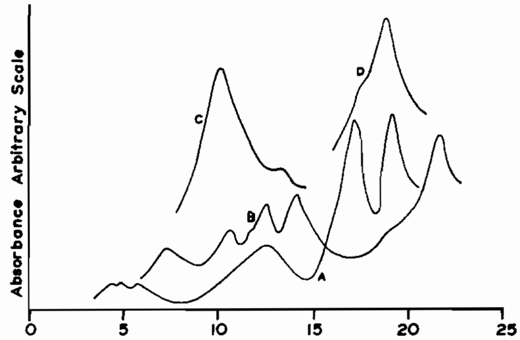


Fig. 1. Diffuse reflectance spectra: [Co(4-*m*-NH$_2$ph-2-pytsc-H)Cl$_2$] (A); [Ni(4-*m*-NH$_2$ph-2-pytsc-H)Cl$_2$] (B); [Cu-(4-*m*-NH$_2$ph-2-pytsc-H)Cl$_2$] (C); [Pt(4-*m*-NH$_2$ph-2-pytsc)Cl] (D).

The spectrum of [Ni(4-*m*-NH$_2$ph-2-pytsc-H)Cl$_2$] is similar to the spectra of known five-coordinate, high-spin nickel(II) complexes, particularly with the spectrum of [Ni(Me$_6$tren)Br]Br for which a distorted trigonal-bipyramidal geometry (C_{3v}) has been proposed [25]. Thus, the spectral bands observed at 7220, 10 526, 12 500, 14 390, 19 230sh and 21 740 cm^{-1} are assigned [26] to $^3E(F) \rightarrow {}^3E(F)$, $^3E(F) \rightarrow {}^3A_2(F)$, $^3E(F) \rightarrow {}^3A_1(F)$, $^3E(F) \rightarrow {}^3A_2(F)$, $^3E(F) \rightarrow {}^3E(P)$ and $^3E(F) \rightarrow {}^3A_2(P)$ transitions, re-

TABLE III. Antitumour Activity of Metal(II) Complexes of 4-*m*-Aminophenyl-2-Formylpyridine Thiosemicarbazone against P388 Lymphocytic Leukaemia Test System in Mice.

Compound	Treatment schedule	Dose mg/kg	Wt. difference (T – C)	T/C (%)
[Co(4-*m*-NH_2ph-2-pytsc-H)Cl_2]	A[a]	200.00	–1.0	87
		100.00	–0.3	87
		50.00	1.1	102
[Ni(4-*m*-NH_2ph-2-pytsc-H)Cl_2]	A	240.00	–3.3	96
		120.00	–0.6	toxic
		60.00	–0.6	87
		30.00	0.3	toxic
		15.00	0.6	97
[Cu(4-*m*-NH_2ph-2-pytsc-H)Cl_2]	B[b]	400.00		toxic
		200.00		toxic
		100.00		toxic
[Zn(4-*m*-NH_2ph-2-pytsc-H)$(OAc)_2$]	C[c]	400.00		toxic
		200.00	–3.7	toxic
		100.00	–1.6	115
[Pt(4-*m*-NH_2ph-2-pytsc)Cl]	A	240.00	–0.9	106
		120.00	0.0	96
		60.00	–1.3	113
		30.00	–0.4	101

[a] Experimental animals were treated 5 times daily with the indicated dose, beginning on day 1 and ending on day 5. [b] Experimental animals were treated once daily with the indicated dose, beginning on day 1 and ending on day 5. [c] Experimental animals were treated twice daily with the indicated dose, beginning on day 1 and ending on day 5.

spectively. In addition to the above transitions a shoulder appears at 11 795 cm^{-1} which is assigned as the spin-forbidden transition, $^3F \rightarrow {}^1D$.

The spectrum of [Cu(4-*m*-NH_2ph-2-pytsc-H)Cl_2] displays two bands at 10 100 and 13 335sh cm^{-1}. This spectrum is similar to that of the trigonal-bipyramidal complex [Cu(Me_6tren)Br]Br, which has a band at 10 300 cm^{-1} with a pronounced shoulder at 13 500 cm^{-1} [27]. Consequently, a five-coordinate configuration is assigned to the complex [Cu(4-*m*-NH_2ph-2-pytsc-H)Cl_2].

The spectrum of [Pt(4-*m*-NH_2ph-2-pytsc)Cl] displays two spectral bands at 17 545sh and 18 870 cm^{-1} which are assigned to metal-to-ligand ($Pt \rightarrow L_{\pi^*}$) charge-transfer transition [28].

Antitumour Activity

The antitumour activity of metal(II) complexes was evaluated at the National Cancer Institute (NCI), Bethesda, Md, according to the standard screening procedure (*cf.* Instruction 14) in the P388 lymphocytic leukaemia test system. The tumour inoculum of 10^6 ascites cells was implanted intraperitoneally on day 0 in $CD_2F_1(CDF_1)$ mice (male). The metal(II) complexes were suspended in saline with Tween 80 and Klucel (hydroxypropylcellulose: Ni(II) complex only) and administered daily in accordance with treatment schedule indicated in Table III. Six mice were used per test compound and the results of screening were evaluated after 30 days on the basis of survival. In a 'survival tumour system' the increase in survival of treated animals over control is expressed as T/C (%) and the compound is considered active when T/C value is greater than 125.

All the complexes showed no significant activity against P388 lymphocytic leukaemia test system in mice. This is a surprising finding because the free compound 4-NH_2ph-2-pytsc-H has excellent antitumour activity *in vivo* against sarcoma 180 ascites cells [8].

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